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► **To cite this version:**

Grégoire Justeau, Chloé Gervès-Pinquié, Marc Le Vaillant, Wojciech Trzepizur, Nicole Meslier, et al.. Association Between Nocturnal Hypoxemia and Cancer Incidence in Patients Investigated for OSA. Chest, 2020, 158 (6), pp.2610-2620. 10.1016/j.chest.2020.06.055 . hal-03150418

HAL Id: hal-03150418

<https://hal.science/hal-03150418>

Submitted on 15 Dec 2022

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Text word count: 3,453

Abstract word count: 253

Association between nocturnal hypoxemia and cancer incidence in patients investigated for obstructive sleep apnea. Data from a large multicenter French cohort.

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Key words: obstructive sleep apnea, intermittent hypoxia, cancer

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Running title: OSA, nocturnal hypoxia and cancer risk

Conflict of interest

The authors declare no conflict of interest associated with this manuscript.

Abstract

Background: Previous studies have yielded inconsistent findings regarding the association between obstructive sleep apnea (OSA) and cancer in humans.

Research Question: Is there an association between indices of sleep-disordered breathing severity and cancer incidence in patients investigated for suspected OSA?

Study Design and Methods: Data from a large multicenter cohort of cancer-free patients investigated for OSA were linked to health administrative data to identify new-onset cancer. Kaplan-Meier survival analysis and Cox proportional-hazards models were used to evaluate the association of cancer incidence with OSA severity and nocturnal hypoxemia.

Results: After a median [inter-quartile range] follow-up of 5.8 [3.8-7.8] years, 718 of 8,748 patients (8.2%) had received a diagnosis of cancer. On unadjusted Kaplan-Meier survival analyses cancer incidence was associated with increasing severity of OSA (Log-Rank Test, $p < 0.0005$) and nocturnal hypoxemia (Log-Rank Test, $p < 0.0001$ for both oxygen desaturation index and % night-time with oxygen saturation $< 90\%$ [T90]). After adjustment for anthropomorphic data, smoking and alcohol consumption, comorbid cardiac, metabolic and respiratory diseases, marital status, type of sleep study, and study site, only T90 was associated with cancer incidence (adjusted hazard ratio [95% confidence interval]: 1.33 [1.05- 1.68] for T90 $\geq 13\%$ versus $< 0.01\%$; $p = 0.02$). On stratified analyses, the association between T90 and cancer appeared stronger in older patients with obesity and no adequate OSA therapy. Among the most frequent cancer sites, nocturnal hypoxemia was associated with lung and breast malignancies.

Interpretation: Nocturnal hypoxemia was associated with all-cancer incidence in patients investigated for OSA. Whether OSA therapy might reduce the risk of cancer needs further evaluation.

Abbreviation list

AHI: apnea-hypopnea index

BMI: body mass index

CI: confidence interval

COPD: chronic obstructive pulmonary disease

Excessive daytime sleepiness: EDS

ESS: Epworth Sleepiness Scale

HR: hazard ratios

INCA: French National Cancer Institute

IH: intermittent hypoxemia

IQR: interquartile range

OSA: obstructive sleep apnea

PAP: positive airway pressure

PMSI: French Hospital Discharge database

PSG: polysomnography

RP: respiratory polygraphy

SD: standard deviation

SNDS: French administrative health care database

T90: percent nighttime with oxygen saturation <90%

Introduction

Recent data from experimental and clinical studies have suggested that obstructive sleep apnea (OSA) might contribute to the development and progression of cancer. Experimental studies in animal models have strongly suggested that intermittent hypoxemia (IH), the hallmark feature of OSA, might promote tumor growth and metastasis. Several putative intermediate mechanisms linking OSA with cancer incidence and prognosis have been proposed including sympathetic over-activity, systemic inflammation, angiogenesis, and immunological alterations (see references¹ for comprehensive review). However, population- and clinic-based studies have yielded inconsistent findings regarding the association between OSA severity and cancer in humans. The epidemiologic study from Nieto et al. was the first to demonstrate a dose–response association between OSA and cancer mortality². Most^{3–5} but not all⁶ subsequent population-based studies reported elevated cancer incidence and/or mortality in subjects with OSA. The Spanish clinic-based cohort study was the first to demonstrate an association between sleep-disordered breathing severity and cancer incidence among patients investigated for clinical suspicion of OSA⁷. The percentage of nighttime spent with oxygen saturation lower than 90% (T90) was the only marker of OSA severity associated with cancer incidence in the entire cohort. Among three subsequent clinic-based studies^{8–10}, two found no association between OSA severity and cancer incidence^{9,10} and one concluded that severe OSA was associated with a higher all-type cancer incidence only in patients under 45 years of age⁸. The above-mentioned studies had some limitations. In several studies the diagnosis of OSA was based on questionnaires or administrative data^{1,4,5}. Most clinic-based studies were monocentric^{8–10}. Several studies included a limited proportion of severe OSA, had a relatively small number of events and/or did not consider competing risk of death from other causes^{2,3,8,9}. In most studies, adjustment was not made for important confounders such as socioeconomic status, alcohol intake or diabetes^{7–9}. Furthermore, in most studies sleep-related oxygen desaturations were assessed with the T90, a surrogate marker of global nocturnal hypoxemia, but not with the oxygen desaturation index (ODI)^{2,3,7,8,10}.

The aim of this large multicenter longitudinal cohort study was to determine whether cancer incidence was independently associated with OSA severity and indices of nocturnal hypoxemia after appropriate adjustment for confounders.

Methods

The study was conducted on the *Pays de la Loire Sleep Cohort*¹¹, linked with data from the French administrative health care database (SNDS), which contains individualized, anonymous, and comprehensive data on health spending reimbursements¹² (see Online Content for details on the *Pays de la Loire Sleep Cohort* and the linkage process with the SNDS database). All patients included in the *cohort* between May 15, 2007 and December 31, 2015 with available SNDS data were eligible for the present study. Patients were excluded if they had received a diagnosis of cancer at any time before the sleep study. Approval was obtained from the University of Angers Ethics Committee and the 'Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé' (CCTIRS; 07.207bis). All patients had given their written informed consent.

Baseline evaluation and questionnaires

Each patient enrolled in the *Pays de la Loire Sleep Cohort* completed surveys including anthropometric data, smoking habits, alcohol consumption, medical history, and medication use (see e-Table 1 for the definition of covariates). Excessive daytime sleepiness and depressive symptoms were assessed by the Epworth score and the QD2A depression score respectively¹³. As previously described, socioeconomic status included the marital status and the occupational category, determined according to the Institut National de la Statistique et des Etudes Economique (INSEE) nomenclature¹¹.

Sleep studies and positive airway pressure treatment

According to French guidelines, patients with a high clinical probability of OSA were investigated by respiratory polygraphy (RP) (CID102L™; CIDELEC, Sainte-Gemmes-sur-Loire, France)¹⁴. Patients with a low likelihood of OSA and/or coexisting sleep disorders received a polysomnography (PSG) (CID102L8D™, CIDELEC, Sainte-Gemmes-sur-Loire, France). Recorded data included nasal-oral airflow

(thermistor and nasal pressure cannula), chest and abdominal wall motion (respiratory inductance plethysmograph belts), arterial oxygen saturation (pulse oximetry), body position and electrophysiological signals for sleep evaluation (PSG). Respiratory events were scored manually using recommended criteria¹⁵. Apnea was defined as an at least 90% decrease in the oronasal thermal sensor signal and hypopnea was defined as an at least 30% decrease in the nasal pressure signal combined with either $\geq 3\%$ arterial oxygen desaturation or an arousal (PSG), both lasting at least 10 s. According to the criteria defined by the French national health insurance, positive airway pressure (PAP) therapy was prescribed in patients with severe OSA and in those with moderate OSA and cardiovascular comorbidities or severe daytime sleepiness. As previously described¹¹, a single home respiratory care company (ALISEO, Beaucozé, France) was involved for PAP device delivery and follow-up support program. Patients were reviewed in consultation by the sleep specialist at 5 months, 12 months then at least annually. Objective daily PAP use was monitored at each follow-up visit and recorded in the database. The average PAP adherence during the follow-up period was calculated to determine treatment status.

Endpoint

The endpoint of the study was all-cancer incidence as defined as the first occurrence of a malignant neoplasm at any time between the sleep study and the final follow-up date of December 31, 2017. The occurrence of cancer was identified on the French Hospital Discharge database (Programme de Médicalisation des Systèmes d'Information [PMSI]), which is linked to the SNDS database¹². Data from SNDS were available from May 2006. The PMSI database provides detailed medical information on all admissions in public and private hospitals, including discharge diagnoses ICD-10 codes and medical procedures performed during the hospital stay. The procedure that we used to identify incident cancers from the PMSI database was adapted from the algorithm developed by the French National Cancer Institute (INCA)¹⁶. The sensitivity, specificity, positive and negative predictive values of the INCA algorithm has been found to be respectively 85.0% (95%CI [84.1-85.9]), 98.5% [98.4-98.6], 90.5% [89.8-91.3], 97.5% [97.3-97.6]. The algorithm was mainly based on primary, related or

associated PMSI diagnostic codes of malignancies (ICD-10: C00-C97, D00-D09, D37-D463). When several admissions occurred for the same patient, only the first hospital stay was considered as reflecting an incident case. The accurateness of PMSI database to identify cancer incidence has been pointed out by previous reports¹⁷⁻¹⁹ who demonstrated a good concordance with data from cancer registries. Patients who did not develop cancer were censored at the date of death or at the final follow-up date.

Statistical analysis

The primary dependent variable of interest was all-cancer incidence. The primary independent variables were OSA severity as assessed by the apnea-hypopnea index (AHI), and two different indices of nocturnal hypoxemia, ODI and T90. In line with recent findings²⁰, the hypoxic burden has also been calculated for a subgroup of our population. Missing values were imputed using a multiple imputation method (MI procedure from SAS) when the proportion of missing values was < 20%. Five datasets were generated using logistic regression for qualitative variables or linear regression for quantitative variables, considering that missing values were random. The baseline differences between OSA categories were compared using the nonparametric Kruskal-Wallis test for quantitative and the chi-square test for qualitative characteristics (see Online Content and e-Table 2 for details on statistical analyses).

Kaplan-Meier survival analysis with log-rank test and Cox proportional hazard models were used to evaluate the association of all-cancer incidence with categories of OSA severity and indices of nocturnal hypoxemia. To adjust for potential confounders, study site and variables for which there was a significant difference between patients with and without incident cancer were entered in the multivariate analysis. The results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). P values for linear trends across categories of OSA severity and indices of nocturnal hypoxemia were calculated by the Cochran-Armitage trend test. The association of continuous forms of AHI, ODI and T90 with cancer incidence was also examined.

To evaluate a potential treatment effect, a stratified analysis was conducted according to treatment status. Patients with no therapy or mean objectively measured PAP adherence <4 h per night during the follow-up period were considered as untreated. Patients with mean objective PAP adherence \geq 4 h per night during the follow-up period were considered as treated. Based on previous reports^{2,7} a priori-defined interactions between exposures and factors that may influence the risk of cancer including age, gender and obesity were also tested. Subgroup analyses were conducted to evaluate the association between of OSA and nocturnal hypoxemia with the most frequent cancer types. Fine and Gray competing-risk regressions were used to account for the competing risk of death²¹.

All statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC). Associations were considered statistically significant for a p value <0.05.

Results

Out of 11,218 patients investigated for suspected OSA between May 15, 2007 and December 31, 2015, 1,644 were not linked to SNDS dataset, 818 had received a diagnosis of cancer before the sleep study and AHI data were unavailable for 8. The final study sample size comprised 8,748 cancer-free patients at the time of the diagnostic sleep study (see Figure 1 and e-Table 3 for baseline characteristics of the entire cohort, the study population, and patients not included).

As shown in Table 1, the study population consisted of typical OSA patients, predominantly male, obese or overweight, frequently presenting cardio-metabolic comorbidities. Among the 8,748 patients included, 1,161 (13.0%) had no OSA, 1,878 (21.5%) had mild OSA, 1,826 (21.0%) had moderate OSA, and 3,883 (44.5%) had severe OSA. As expected, patients with increasing OSA severity were of significantly higher age and BMI, and were more frequently male with medical history of diabetes, hypertension, cardiac disease and alcohol consumption. There were also significant differences between OSA categories for smoking habits, socio-professional status and the type of sleep recording. The comparison of patients with and without incident cancer showed significant differences for age, gender, body mass index, smoking status, alcohol intake, diabetes,

hypertension, medical history of cardiac and chronic obstructive pulmonary disease, indices of OSA severity, Epworth score, marital status, and type of sleep study (e-Table 4).

After a median (interquartile range [IQR]) follow-up of 5.8 [3.8-7.8] years, 718 patients (8.2%) had received a diagnosis of malignancy. Colorectal (n=129), lung (n=69), prostate (n=66) and breast (n=62) were the most common incident cancer sites. As shown in table 1, the incidence of cancer increased from 5.7 to 9.1% (p=0.0005) between the non OSA group and the severe OSA group (incidence density rates: 10.0 to 16.6 per 1000 person-years). Unadjusted Kaplan-Meier survival curves indicating cancer-free survival according to categories of OSA severity, quartiles of ODI and T90 are shown in Figure 2. Log-rank tests comparing curves showed that cancer-free survival was negatively associated with increasing severity of OSA (p<0.0005) and nocturnal hypoxemia (p<0.0001 for both ODI and T90).

Cox proportional hazard models demonstrated a significant association between all-cancer incidence and increasing nocturnal hypoxemia assessed by T90. Compared with the lowest severity category, the adjusted HR, 95% [95%CI] for incident cancer was 1.33 [1.05- 1.68] for T90 \geq 13% *versus* <0.01%; p=0.02). Cancer incidence was not associated with OSA severity and ODI after adjustment for confounders (Table 2). As shown in e-Table 5, all-cancer incidence was associated with continuous forms of AHI, ODI, and T90 but the association was no longer significant after adjustment for confounders.

Hypoxic burden data were available in 5,683 patients. Slight but significant differences were observed between the entire cohort and the subgroup of patients with hypoxic burden measurement (e-Table 6). As shown in Table 3, increasing hypoxic burden was associated with a higher incidence of cancer but the association was no longer significant after adjustment for confounders.

Cox proportional hazard models assessing the association between all-cancer incidence and T90 were then conducted separately in 5,724 untreated patients with no active OSA therapy or PAP adherence <4 h per day (median [IQR]: 2.4 [1.0-3.4] h per day), and 3,024 treated patients with

objective PAP adherence ≥ 4 h per day (median [IQR]: 6.5 [5.5-7.5] h per day). As expected, patients receiving adequate PAP therapy had more severe disease compared to untreated patients (e-Table 7). As shown in Figure 3, there was a dose-response relationship between T90 and all-cancer incidence in the entire study population ($p=0.04$ for linear trend) and in untreated patients ($p=0.004$ for linear trend), but not in patients with adequate PAP therapy (p value for interaction = 0.39). There was no association of all-cancer incidence with OSA severity ($p=0.54$ for linear trend) and quartiles of ODI ($p=0.88$ for linear trend) in untreated patients (data not shown).

Further stratified analyses evaluating the association between cancer incidence and severe nocturnal hypoxemia are presented online in e-Figure 1. The association was stronger among patients aged > 60 years compared with those aged ≤ 60 years ($p < 0.0001$ for interaction). The association between severe nocturnal hypoxemia and cancer incidence appeared also stronger among patients with obesity but the interaction was not statistically significant ($p=0.89$).

Subgroup analyses demonstrated a dose-response association between nocturnal hypoxemia and incident lung cancer ($p=0.03$ for linear trend). Breast cancer was associated with the second (adjusted HR 2.04 [1.04-3.98]; $p=0.04$), but not with third or fourth quartiles of T90 as compared with the first quartile. Colorectal and prostate malignancies were not associated with nocturnal hypoxemia (Table 4).

The magnitude of the association between all-cancer incidence and T90 was unchanged after controlling for a competing risk of death (e-Table 8).

Discussion

The main finding of our study is that T90, a marker of overnight hypoxemia predicts all-cancer incidence in patients investigated for suspected OSA, independently of major confounding factors. Previous cohort studies have demonstrated an independent association between T90 and cancer mortality² or incidence⁷. Conversely, recent data from a large cohort of 10,149 patients with suspected OSA, have shown no independent association between cancer incidence and AHI or T90¹⁰. However, several characteristics of the study population may have contributed to these negative

findings including younger age and lower OSA severity. Altogether our findings and those from previous studies^{2,7} suggest that hypoxia may be the main intermediate mechanism linking OSA to cancer. In the present study, cancer incidence was associated with T90 but not with ODI, which is considered the best marker of IH in clinical setting. Whether IH can directly or indirectly induce tumorigenesis has not been clearly established, but current evidence strongly suggests that IH enhances cancer progression in animal models¹. However, using FiO₂ of about 5% or less, animal models of IH reproduces severe forms of the human OSA. In mice exposed to chronic IH, the degree of metabolic dysregulation is dependent on the severity of the hypoxic stimulus²². Our findings and those from the Spanish clinic-based cohort study⁷ suggest that T90 would be a better predictor of cancer risk than AHI and ODI, as it has also been demonstrated for atrial fibrillation, cardiovascular events and all-cause mortality^{23,24}. As previously discussed⁷, these findings might be explained by the fact that a significant proportion of respiratory events taken into account in the calculation of AHI and ODI are accompanied by small drops in oxygen saturation resulting in low T90. The T90 characterizes not only IH resulting from obstructive events but also persistent hypoxemia, such as from COPD, obesity hypoventilation or cardiac failure. In the present study, the association between T90 and cancer incidence remained statistically significant after adjustment for BMI, cardiac diseases and COPD. However, as pulmonary function tests and arterial blood gases were not available in our database, the contribution of comorbid cardiac and respiratory disorders cannot be excluded.

A recent study identified the hypoxic burden as an independent predictor of cardiovascular mortality²⁰. While a strong association was found between hypoxic burden and cardiovascular mortality, there was a weaker association with all-cause mortality suggesting that there may be a distinct biological pathway linking OSA-related hypoxemia to cardiovascular death. In the present study, we found no independent association between hypoxic burden and cancer incidence. It is important to note that the hypoxic burden does not distinguish short and deep desaturations from and long and shallow ones. The hypoxic burden was found to be poorly correlated with T90 and its

association with conventional polysomnographic indices weakened for patients with moderate to severe OSA²⁰.

On stratified analysis, Cox proportional hazard models assessing the association between T90 and cancer incidence showed a significant dose-response relationship in untreated patients, but no association in patients receiving adequate PAP therapy of OSA. Furthermore, the association between T90 and cancer risk was stronger in untreated patients than in the entire cohort. However, taking into account unbalanced sample sizes, the observational design of our study, the healthy adherer effect^{25,26}, and the fact that formal tests for interaction did not reach statistical significance, our finding should not be interpreted as the demonstration of a preventive effect of PAP therapy on cancer incidence. Further studies are required to evaluate whether adequate OSA therapy might reduce the risk of cancer in patients with marked nocturnal hypoxemia.

Our finding that severe nocturnal hypoxemia was significantly associated with cancer risk in patients with obesity but not in non-obese subjects is consistent with previous data underlying the interaction between obesity, nocturnal oxygen desaturations and cardiovascular risk²⁷. It has been demonstrated that body weight is a significant predictor of the amount of oxygen desaturation during apnea's and hypopnea's, potentially exacerbating the adverse health impact of OSA in obese individuals²⁸. We observed that the association between T90 and cancer incidence was stronger in older patients contrary to the Spanish cohort study, which however included a relatively small sample of older subjects (n=1,203)⁷. The result from these stratified analyses need to be interpreted with caution due to limited and/or unbalanced sample sizes.

In line with previous reports^{6,7,29-31}, we found that among the most frequent cancer sites, nocturnal hypoxemia was associated with the incidence lung and breast cancer but not with colorectal and prostate malignancies. A significant association between oxygen desaturation and the incidence of smoking-related cancers have been found in previous clinic-based cohort studies^{7,10}. Sleep apnea and nocturnal hypoxemia were associated with an increased prevalence of lung cancer in a recent cross-sectional study²⁹. Li et al. recently reported that OSA severity was a risk factor that contributed to

short overall survival in patients with lung cancer³¹. The authors identified molecular convergence between hypoxia and lung cancer that reflected their clinical profiles and revealed molecular pathways involved in hypoxic-induced lung cancer progression. The reasons why breast cancer risk was increased in patients with mild nocturnal hypoxemia but not in those with more severe oxygen desaturation remain unclear and the interpretation may be limited by sample size. Further studies are required to determine whether the presence OSA and nocturnal desaturation may affect all types of oncological conditions or only selective types of tumors.

The strength of the current study includes a multicenter design, a large sample size with a wide range of sleep-disordered breathing severity, an appropriate adjustment for multiple cancer risk factors, a long and complete follow-up with access to comprehensive data from the National Health Insurance Information System, and the assessment of different measures of hypoxia. The French Health Care database now covers 98.8% of the French population, over 66 million persons, from birth (or immigration) to death (or emigration)³². The linkage between clinical cohort's data and SNDS data makes easier the long-term follow-up with limited attrition bias contrary to trials^{33,34}. Our study also has limitations. Because of its observational design, potential unmeasured confounding factors cannot be excluded. We also acknowledge that sleep recordings were performed either by PSG or RP and manually scored locally, with no assessment of inter-scorer reliability. It cannot be excluded that inter-scorer variability, particularly for hypopneas which did not cause an oxygen desaturation³⁵ may have contributed to the lack of association between cancer incidence and categories of OSA severity. However, this potential bias was mitigated by the adjustment for study site. Furthermore, our finding that T90 was a better predictor of cancer risk than AHI is consistent with previous reports⁷. There are some limitations related to the use of health administrative data. We had no data about cancer stage and the time from cancer symptom onset to diagnosis. In French hospitals, all physicians routinely contribute to PMSI data collection, with annual quality control of coding resulting in a decreased risk of misclassification bias¹². Furthermore, previous studies have demonstrated that the use of PMSI claims database was a suitable approach to estimate cancer incidence^{17,18,33,36}. We acknowledge that

our study did not have sufficient statistical power to examine the association of OSA and nocturnal hypoxemia with the different cancer subtypes. Finally, the fact that hypoxic burden data were not available in the entire cohort may have also decreased the power to detect a significant association with cancer incidence.

Interpretation

Nocturnal hypoxemia was associated with all-cancer incidence in patients investigated for suspected OSA. Whether OSA therapy might reduce the risk of cancer needs to be further evaluated.

Acknowledgments

We thank the National Health Insurance Fund for giving us access to the French administrative health care database.

The *ERMES study group*: Centre Hospitalier Universitaire, Angers: Christine Person, Pascaline Priou; Centre Hospitalier, Le Mans: Olivier Molinier, Audrey Paris; Centre Hospitalier, La Roche sur Yon: Isabelle Caby, Maël Bellier; Pôle santé des Olonnes, Olonne sur Mer: Marie Langelot-Richard; Centre Hospitalier Universitaire, Nantes: Sandrine Jaffre, Frédéric Corne; Nouvelles Cliniques Nantaises: Marc Normand de la Tranchade; Centre Hospitalier, Machecoul: Béatrice Rouault; Institut Recherche

Guarantor's name

Prof Gagnadoux is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Author Contributions

G.J., C.G.-P., M.L.V., W.T., N.M., F.Gou., T.P., X.-L.N., L.L.V., P.M., A.B.-T., M.-P.H., C.G., M.B., T.U., F.Gag. were substantially involved in the design of the study and critical revision of the paper for important intellectual content.

G.J., C.G.-P., M.L.V., T.U., F.Gag. were substantially involved in drafting the article.

All authors were substantially involved in data acquisition, data analysis, or interpretation of data. All authors approved this final version of the article.

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Figure Legends

Figure 1: Flow diagram of the subjects during the study

Figure 2: Unadjusted Kaplan-Meier survival curves indicating the time to incidence of cancer grouped by categories of obstructive sleep apnea (OSA) severity (Figure 2A), quartiles of oxygen desaturation index (ODI) (Figure 2B), and percent night-time with oxygen saturation below 90% (T90) (Figure 2C). The log-rank test was used to compare the survival distribution across categories.

Figure 3: Cox proportional hazard models assessing the association between nocturnal hypoxemia and all-cancer incidence depending on obstructive sleep apnea treatment status.

Abbreviations: HR, hazard ratio; CI, confidence interval.

* $p < 0.05$ versus the reference group; ** $p < 0.01$ versus the reference group

†Tested by the Cochran-Armitage trend test.

$P = 0.39$ for the interaction of treatment status and T90 for all-cancer incidence.

HR were adjusted for *Adjusted for age, gender, body mass index, smoking status, alcohol intake, diabetes, hypertension, medical history of cardiac and chronic obstructive pulmonary disease, marital status, type of sleep study, and study site.

Table 1: Characteristics of the study population according to categories of obstructive sleep apnea (OSA) severity.

	All	No OSA	Mild OSA	Moderate OSA	Severe OSA	p value*
n	8,748	1,161	1,878	1,826	3,883	
Age, years	61 [51-70]	52 [41-63]	58 [49-63]	61 [52-70]	64 [55-72]	<0.0001
Men, %	64.5	49.4	56.3	66.4	72.0	<0.0001
BMI, kg/m ²	29 [26-34]	26 [23-30]	28 [25-30]	28 [26-33]	32 [28-36]	<0.0001
Alcohol intake, g/day	0 [0-20]	0 [0-10]	0 [0-10]	0 [0-20]	10 [0-20]	<0.0001
Smoking status, %						
Never	41.6	42.5	42.8	41.6	40.6	<0.0001
Current	22.6	28.2	24.4	21.2	20.7	
Former	35.9	29.3	32.9	37.2	38.7	
Epworth sleepiness score	10 [6-14]	10 [3-14]	9 [6-14]	10 [6-14]	10 [6-14]	0.4009
QD2A depression score	3 [1-6]	3 [1-6]	3 [1-6]	3 [1-6]	3 [1-6]	0.1876
Diabetes, %	14.5	6.2	10.3	13.1	19.5	<0.0001
Cardiac disease, %	10.4	5.4	9.1	10.5	12.4	<0.0001
Hypertension, %	33.9	15.7	28.0	31.4	43.2	<0.0001
COPD, %	9.1	8.2	8.9	8.3	9.8	0.1819
AHI, events/h	24 [9-41]	2 [1-3]	9 [7-3]	21[18-24]	44 [35-59]	<0.0001
ODI, events/h	17 [6-35]	2 [1-5]	7 [4-5]	15 [9-21]	37 [24-55]	<0.0001
T90, %	2 [0-13]	0 [0-0]	0 [0-0]	1 [0-5]	10 [2-28]	<0.0001
Occupational category, %						
Farmer	4.2	2.7	3.2	3.6	5.4	<0.0001
Craftsman	9.6	7.3	8.7	9.3	10.8	
Executive	19.2	17.4	19.5	22.1	18.2	
Intermediate	21.3	25.1	21.6	21.9	19.8	
Employees	19.6	24.8	23.0	18.3	17.0	
Workers	26.1	22.8	24.0	28.7	28.7	
Married or living as a couple, %	78.1	75.5	79.7	78.2	78.0	0.0673
PSG, %	42.5	44.5	47.0	56.3	33.3	<0.0001
Follow-up time, person-years	47,909	6,583	10,219	9,787	21,322	0.0089
Incident cancers, n	718	66	136	161	355	<0.0001
All-cancer incidence, n (%)	8.2	5.7	7.2	8.8	9.1	0.0005

Data are expressed as median [interquartile range], n or percentages

Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease; AHI, apnea-hypopnea index; ODI, 3% oxygen desaturation index; T90, percent night-time with oxygen saturation below 90%; PSG, polysomnography.

* OSA categories were compared using the nonparametric Kruskal- Wallis test for quantitative and the chi-square test for qualitative characteristics.

Table 2: Cox proportional hazard models assessing the association of all-cancer incidence with categories of obstructive sleep apnea (OSA) severity and indices of nocturnal hypoxemia.

	Follow-up time, person-years	All-cancer incidence, n (%)	Adjusted* hazard ratios [95%CI]	p value
Categories of OSA severity				
No OSA (ref)	6, 582	66 (5.7)	1.00	-
Mild OSA	10, 219	136 (7.2)	1.01 [0.76-1.33]	0.9714
Moderate OSA	9,787	161 (8.8)	1.13 [0.91-1.40]	0.2582
Severe OSA	21, 322	355 (9.1)	1.20 [0.98-1.47]	0.0754
3% Oxygen desaturation index				
<6.1 events/ h (ref)	11, 965	125 (5.8)	1.00	-
6.1 to <17.0 events/h	10, 386	165 (8.5)	1.16 [0.92-1.48]	0.2102
17 to <35.6 events/h	11, 360	188 (8.7)	0.99 [0.78-1.26]	0.9200
≥35.6 events/h	11, 285	202 (9.8)	0.93 [0.72-1.20]	0.5628
% night-time with oxygen saturation<90%				
<0.01 % (ref)	17,069	163 (5.2)	1.00	-
0.01 to <2.1%	7,386	121 (8.9)	1.32 [1.04-1.69]	0.0250
2.1 to <13%	10,881	182 (9.2)	1.22 [0.97-1.53]	0.0864
≥13 %	11,844	244 (11.3)	1.33 [1.05- 1.68]	0.0183

Abbreviations: CI, confidence interval

*Adjusted for age, gender, body mass index, smoking status, alcohol intake, diabetes, hypertension, medical history of cardiac and chronic obstructive pulmonary disease, marital status, type of sleep study, and study site.

Table 3. Cox proportional hazard models assessing the association between hypoxic burden and cancer incidence (n= 5,683)

	Follow-up time, person-years	All-cancer incidence, n (%)	Unadjusted HR [95%CI]	p value	Adjusted* HR [95%CI]	p value
Hypoxic burden						
<12 %min/h (ref)	7,306	76 (5.5)	1.00	-	1.00	-
12 to <36 %min/h	7,421	110 (7.9)	1.41 [1.05-1.88]	0.0220	1.10 [0.81-1.48]	0.5364
36 to <84 %min/h	7,260	119 (8.6)	1.56 [1.17-2.08]	0.0024	1.01 [0.74-1.36]	0.9763
≥84 %min/h	7,634	145 (10.5)	1.83 [1.38-2.41]	<0.0001	0.92 [0.68-1.25]	0.5991

Abbreviations: HR, hazard ratio; CI, confidence interval

*Adjusted for age, gender, body mass index, smoking status, alcohol intake, diabetes, hypertension, medical history of cardiac and chronic obstructive pulmonary disease, marital status, type of sleep study, and study site.

Table 4. Cox proportional hazard models assessing the association of nocturnal hypoxemia (percent night-time with oxygen saturation below 90% [T90]) with the incidence of different cancer sites.

	Follow-up time, person-years	All-cancer incidence, n (%)	Unadjusted HR [95%CI]	Adjusted* HR [95%CI]	p value for linear trend #
Incident lung Cancer (n=72)					
T90, %					
<0.01 (ref)	16 556.5	12 (0.40)	1.00	1.00	0.0349
0.01 to <2.1	7 040.81	9 (0.73)	1.77 [0.75-4.20]	1.07 [0.41-2.76]	
2.1 to <13	10 321.16	15 (0.83)	2.02 [0.95-4.32]	1.29 [0.58-2.86]	
≥13	11 137.86	36 (1.84)	4.47 [2.32-8.59] +++	2.14 [1.01-4.54] †	
Incident breast cancer (n=67)					
T90, %					
<0.01 (ref)	6 986.35	20 (1.55)	1.00	1.00	0.7989
0.01 to <2.1	2 653.35	19 (4.02)	2.52 [1.35-4.73] ++	2.04 [1.05-3.98] †	
2.1 to <13	3 239.83	16 (2.79)	1.74 [0.90-3.36]	1.40 [0.69-2.87]	
≥13	3 214.7	12 (2.06)	1.31 [0.64-2.67]	1.14 [0.50-2.58]	
Incident colorectal cancer (n=131)					
T90, %					
<0.01 (ref)	16 625.66	32 (1.06)	1.00	1.00	0.5105
0.01 to <2.1	7 064.47	21 (1.68)	1.55 [0.89-2.69]	1.18 [0.67-2.09]	
2.1 to <13	10 376.26	38 (2.08)	1.91[1.19-3.05] ++	1.25 [0.76-2.06]	
≥13	11 160.47	45 (2.29)	2.10 [1.33-3.30] ++	1.19 [0.70-2.01]	
Incident prostate cancer (n=68)					
T90, %					
<0.01 (ref)	9 648.8	13 (0.75)	1.00	1.00	0.6268
0.01 to <2.1	4 466.37	13 (1.65)	2.16[1.00-4.66] †	1.49 [0.67-3.30]	
2.1 to <13	7 152.52	18 (1.45)	1.86 [0.91-3.81]	1.13 [0.54-2.38]	
≥13	7 903.23	24 (1.74)	2.25[1.15-4.43] †	1.33 [0.62-2.84]	

Abbreviations: HR, hazard ratio; CI, confidence interval

*Adjusted for age, gender, body mass index, smoking status, alcohol intake, diabetes, hypertension, medical history of cardiac and chronic obstructive pulmonary disease, marital status, type of sleep study, and study site.

† p<0.05; ++ p<0.01; +++ p<0.0001

Tested by the Cochrane-Armitage trend test.

11,218 patients from the *Pays de la Loire Sleep Cohort*, investigated by overnight polysomnography or overnight respiratory polygraphy for suspected obstructive sleep apnea between May 15, 2007 and December 31, 2015

No linkage with data from the French National Health Insurance Information System (n=1,644)

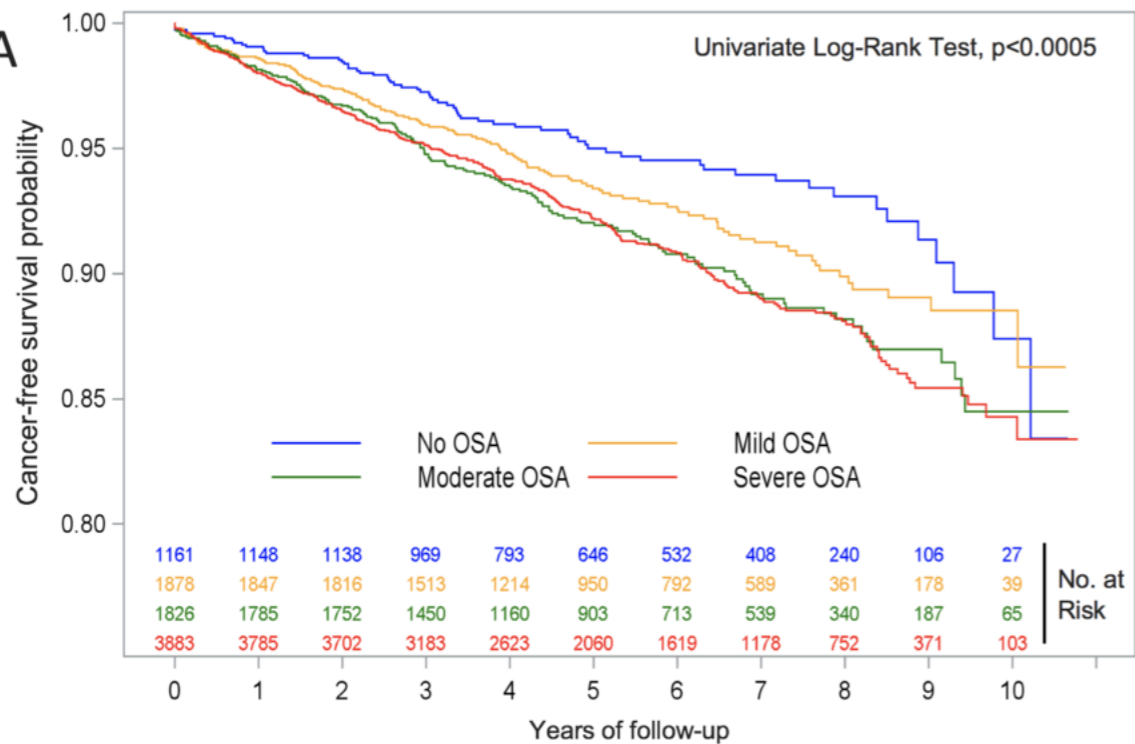
9,574 patients with available data from the French National Health Insurance Information System

826 patients excluded due to:

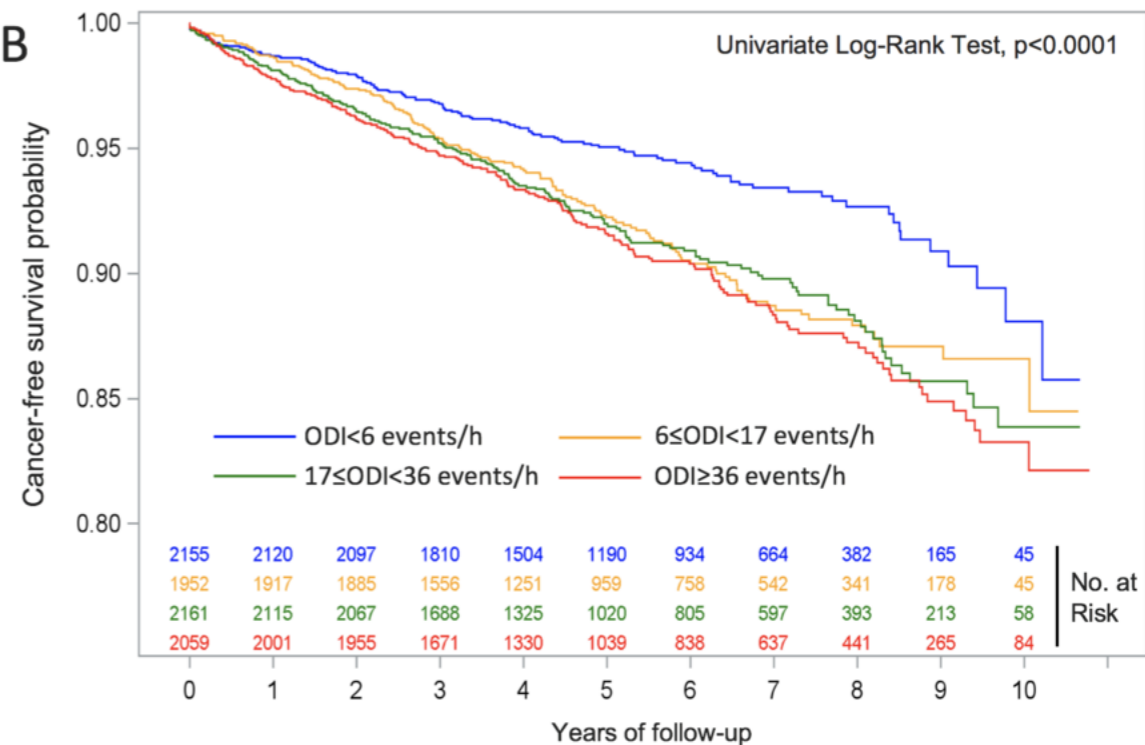
- Cancer diagnosis prior to sleep study (n=818)
- Unavailable apnea-hypopnea index (n=8)

8,748 patients analyzed

2A



2B



2C

